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(21) International Application Number: PCT/GB97/02705 (22) International Filing Date: 1 October 1997 (01.10.97) (30) Priority Data: 9620752.7 4 October 1996 (04.10.96) GB (71) Applicant (for all designated States except US): DYTECH CORPORATION LTD. [GB/GB]; Stopes Road, Stannington, Sheffield S6 6BY (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): SMITH, Robert, Terence [GB/GB]; 103 East Bawtry Road, Brecks, Rotherham S60 4BX (GB). SAMBROOK, Rodney, Martin [GB/GB]; 11 Brookfields, Calver, Sheffield S30 1XA (GB). (74) Agent: SHAW, Laurence; Laurence Shaw & Associates, Metropolitan House, 5th floor, 1 Hagley Road, Edgbaston, Birmingham B16 8TG (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PRODUCTION OF POROUS ARTICLES		
(57) Abstract		
An aqueous dispersion of ceramic particles and containing a polymerisable monomer was foamed before polymerisation, e.g. using a catalyst and initiator, was started.		

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PRODUCTION OF POROUS ARTICLES

The invention relates to the production of articles of controlled porosity.

In our European patent B-0598783 (Agent's ref: P00914EP) there is described and claimed a method of making a porous refractory article composed of refractory particles, the method comprising the steps of:

- a) forming a dispersion comprising particles in a liquid carrier and containing a polymerisable monomeric material
- b) introducing gas into the dispersion,
- c) polymerising the foamed structure,
- d) drying, to remove the liquid carrier to provide a solid article having pores derived from the bubbles; and
- e) firing to remove the organic binder and to provide a ceramic bond.

Preferably the monomeric material is selected to polymerise by cross linking, whereby the liquid carrier and ceramic particles are held within the polymerised structure.

The method of this prior patent is arranged to produce a variety of useful articles such as catalyst supports, flame supports; gas filters; air fresheners; ceramic armour; diesel particulate traps; insulation materials; artificial parts for the body; metal filters, reusable filters; liquid filters; storage and transportation for flammable and/or toxic materials,

humidity sensors, chromatography; filter candles for filtration of hot combustion gases, diaphragms, membranes, refractory separators, phase dividers and electrolytes for high temperature fuel cells.

In our patent publication WO95/30631 (PCT/GB95/01063, Agents Ref. P01204PCT) there is described and claimed a method of making a porous refractory article, the method comprising the steps of:

- forming an aqueous dispersion of refractory particles including a polymerisable monomer component which on polymerisation generates an exotherm
- adding a thermally activated gas generating substance
- adding agents such as initiator and/or catalyst to cause the polymerisation
- adjusting the temperature and/or pressure so that the gas generating substance generates the gas before or during the initial stage of polymerisation of the monomer component whereby the gas forms bubbles which under the heat of the exotherm interconnect to form an interconnected open pore structure.

By controlling the temperature and pressure the decomposition rate of the gas generating substance is controlled. This in turn provides a means of controlling the density of the end product.

It is one object of the invention to provide a method of making a porous article having controlled levels of porosity, interconnectivity, pore size, and mechanical properties suitable for use in various applications.

In one aspect the invention provides a method of making a porous article composed of bonded particles, the method comprising the steps of:

- a) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
- b) forming a foam of the dispersion;
- c) polymerising the foamed structure;
- d) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles, and
- e) firing the article to remove the organic binder and provide a ceramic bond

characterised in that small bubbles of gas are introduced in the dispersion with agitation to form the foam and are allowed or caused to coalesce before the polymerisation.

The dispersion comprises particles having an average particle size less than about 5 micrometres and preferably 95% of the particles will be less than about 2 micrometres.

If the particles are larger than this size than the particles tend to settle or sediment. However, the particles can be much larger, say 100 micrometres or more, in which case agents will be present to control undesired settling; polymerisation of monomers is a suitable means of preventing settling. The particles will be chosen according to the intended end use. As will be explained later, for the preferred use hydroxyapatite is present either alone or with other particles. The other particles can include both oxides and non-oxides such as alumina, mullite, silicon carbide, silicon nitride, zirconia, titanium oxide and the like.

The content of the solids in the dispersion will tend to be about 10% by weight as a minimum and about 90% by weight as a maximum; a preferred range is from about 40% to about 80% by weight.

Conveniently the liquid carrier is water but it may be organic, e.g. alcohol, glycol or the like; or a mixture.

In order to produce a dispersion with the required solids loading and a suitable rheology, it is preferred to add dispersing agents to the suspension. The dispersing agents are commonly used throughout the ceramic industry and suitable agents in each case can be determined by the man skilled in the art. The colloidal stability may be controlled by the adjustment of the pH, in addition to or alternating to the dispersion agents.

Advantageously surfactants (which can be cationic, anionic or non-ionic) are present in the dispersion. In low viscosity systems where the ability of a system to foam is controlled by the surface tension, the surfactant type and concentration can have a direct influence not only on the level of porosity within the system but also the pore size and the interconnectivity. The concentration of surfactant can be used to influence the bubble size within a foam and the rate of coalescence, both of which can be used to influence the final pore size.

By controlling the rheology of the suspension it is possible to influence the rate of coalescence of the foam structure. A slurry which exhibits a low degree of pseudoplasticity coupled with a low bulk viscosity is susceptible to foam collapse and rapid bubble growth. In contrast a slurry which exhibits a high degree of pseudoplasticity is subject to long term stability and a less rapid bubble growth although at an acceptable level. As the bulk viscosity of the system increases the controlling effect of the surfactant diminishes.

Another factor which influences the growth of the foam structure is the period before the onset of polymerisation. This period can be controlled by the addition levels of the initiator and catalyst. By controlling these levels as well as the oxygen concentration within the foaming gas the length of time before polymerisation starts can be controlled between an instantaneous polymerisation and one which starts after a period, which can be up to 20 minutes or more. Our evaluations suggest that this period has a major influence on cell structure where the porous article is to be used as a bone substitute.

In a further feature of the invention the process of increasing the cell size within a foam can be encouraged by the application of a partial vacuum to a foam before the commencement of polymerisation until after the end of polymerisation. At the end of polymerisation the stable foam is brought back to atmospheric pressure. This additional step to the foaming process can be used to increase the rate at which the final desired large cell size can be achieved.

Other additives may be present, e.g. viscosity control agents, reinforcing fibres or particles, retarders for polymerisation; and the like.

The bubbles of gas may be introduced in any convenient way, although the preferred methods are listed in our previous patent. The gas used for foaming can be air, although an inert foaming gas such as nitrogen or argon is preferred. To produce a foam with a large pore structure and a high degree of porosity, one could either introduce bubbles of the correct size and quantity into the suspension or cause smaller bubbles to grow by a process of coalescence. The latter is preferred at the moment.

In order to produce the small bubbles within the foam mechanical agitation is preferred.

Our investigations have shown that the structure of the foam can be broken into four distinctly different areas:

- the cells or bubbles

- the struts
- the windows, and finally
- the particulate microstructure

These structures can be seen in Figure 1 of the accompanying drawings and are explained as follows.

A number of cells can be seen in the left hand photo in Figure 1. These cells are formed as a result of introducing a gaseous phase into the ceramic suspension. Where these cells touch there is a tendency for the cell to change shape to maximise the packing density and for the slurry to drain from the point of contact towards the strut.

A strut can be seen in the top right hand photo in Figure 1. These struts are the building block for the foam structure. At the point of contact between each cell a thin film of liquid exists. During the later gelling and binder burnout steps this film is removed to leave what we call the cell "windows". These are the connecting holes which interlink adjacent cells and can be clearly seen in the left hand photo in Figure 1.

The final structure is that which forms the cell walls and struts.

It is a feature of the invention that the final articles formed consist essentially of the starting ceramic materials only, so avoiding the need for the removal of residual secondary e.g. inorganic binders. The article can thus consist of ingredients acceptable for medical use, e.g. as bone grafts for orthopaedic, surgical, dental and like uses both for humans and animals. There will always be a need to replace bone lost as a consequence of traumatic or non-traumatic events. Bone substitute materials are

available and approved for clinical use. These materials have been successfully used in orthopaedics, dentistry and facial plastic surgery. Among the types of bone graft materials used, particular interest has been shown in the porous types which can provide a scaffold for in growth of connective tissue and bone. Studies have shown that pore sizes less than 10 micrometre prevent ingrowth of cells, pore sizes of 15 to 50 micrometre encourages fibrovascular ingrowth; pore sizes of 50-150 micrometre result in osteoid formation; and pore sizes greater than 150 micrometre facilitate the ingrowth of mineralized bone. Different approaches have been taken to try and mimic the hydroxyapatite frame work within both the cortical and cancellous bone. One material is based on the conversion of a coralline structure to hydroxyapatite material. With this process the selection of the coral with the correct pore structure is imperative before conversion takes place. Two corals were eventually selected exhibiting two different pore structures. These two pore structures are intended to replicate the different structures in cortical and cancellous bone. It is a feature of this invention that synthetic articles made by the method may be used as bone graft materials of high acceptability.

Hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ is an ideal candidate starting material. This material belongs to a group of calcium phosphates which are being considered as bone substitute materials. The invention is applicable to hydroxyapatite and any other calcium phosphate (where the Ca/P atomic ratio may vary widely). In addition to this group of materials it may be advantageous to create an interconnected structure in another ceramic material such as alumina or zirconia for mechanical property reasons and either use the material as produced, or coated with a more bioactive material such

as hydroxyapatite. It is another feature of this invention that the materials known as "Bioglass" could be converted in highly porous structures using this method.

The polymerisation preferably proceeds by crosslinking of reactive organic monomers. Examples include acrylates, such as ammonium acrylate or hydroxyethyl methacrylate; or the like. Preferably the monomers are dissolved in water or other liquid carrier to give a premix solution. To this solution are added an initiator and either heat or a catalyst are used to induce free radical vinyl polymerisation. In another variation, the dispersion includes a monosaccharide such as galactose, which can be condensed to form a dimer, trimer or polymer, to have the same effect.

The foamed composition may be allowed or caused to acquire sufficient green strength to allow it to be moved from the parent container or mould. The composition may be subjected to drying to drive off the liquid. In the case of water, drying can be carried out below about 100°C in an oven or using high frequency drying equipment.

The pore sizes in the formed article can be controlled remarkable uniform to yield a material with a pre-determined pore size and level of interconnectivity. The true porosity may range from about 20% to about 95%. The article formed is relatively robust after polymerisation and strong enough to be machined after removal of the liquid carrier.

The firing temperature and duration are selected according to the nature of the particles, e.g. alumina generally requires a higher sintering temperature than hydroxyapatite.

In one more specific aspect the invention provides a method of making a porous article composed of bonded particles, the method comprising the steps of:

- a) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
- b) forming a foam of the dispersion;
- c) polymerising the foamed structure
- d) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles, and
- e) firing the article to remove the organic binder and provide a ceramic bond.

characterised in that small bubbles of gas are introduced in the dispersion with agitation to form the foam and are allowed or caused to coalesce before the polymerisation, and in that the firing is carried out at a temperature appropriate to the growth of bone cells.

It is a feature of this invention to provide an article having a highly microporous structure if the sintering procedure is controlled. This microporous structure can have advantages in certain applications e.g. it may be infilled with certain drugs such as

antibiotics or growth factors, to act as a slow release agent at the site of an implant and it appears to encourage the easy attachment of in-growing bone cells compared to a dense microstructure.

The formed article may be in a variety of shapes, e.g. in the form of granules, bars, cylinders or rods, blocks or the like.

In order that the invention may be well understood it will now be described by way of illustration only by reference to the following examples and micrographs:

Example I

Hydroxyapatite powder, ammonium acrylate monomer, methylenebisacrylamide, water, the ammonium salt of polyacrylate and the ammonium salt of polymethacrylate were mixed together to form a slurry which was subjected to a high shear mixer in order to remove any agglomerates within the slurry. This was transferred to a glove box within which the oxygen concentration was approx. 0.1%. A surfactant TERGITOL TMN10 was introduced into the slurry and the whole was agitated in a mixer designed to introduce air so that a foam will be formed. The amount by which the ceramic solid is foamed is dependant on the final density required, the solids content of the slurry and the shrinkage which will occur at the later stages of drying and firing. The amount of surfactant added determines the extent of foaming, and this was selected to achieve the required final density. Once the foam density was achieved, ammonium persulphate (initiator) and tetramethylethylenediamine (catalyst)

were injected into the foam to cause the acrylate monomer to start to polymerise. The time before the onset of polymerisation was about 1.5 minutes.

The mixture was restirred and allowed to stand. Polymerisation began after about 1.5 minutes. A photo of the microstructure produced after an idle time of 1.5 minutes is shown in Figure 2. Once polymerised the foam was removed from the mould and allowed to dry at room temperature for 2 days before being forced dried at 60° C in an oven.

At this point the "green" ceramic can easily be machined into the desired shape. The "green" article was heated in a furnace to remove the organic binder and to cause the ceramic microstructure to densify. The sample was split in two and fired at two different temperatures. Sample 1 shown in Figure 3 and sample 2 in Figure 4 were fired at 1250° C for 2 hrs and 1350° C for 2 hrs respectively. It can be seen that the degree of microstructural densification can be adjusted with the sintering conditions. Sample 1 exhibits a highly connected microstructure whereas the microstructural porosity has been removed in sample 2. Live human bone cells were cultured. Both samples 1 and 2 were immersed in the cultures and Figures 5 and 6 show the results after 36 hrs immersion for sample 1 and 2 respectively. The bone cells can be clearly seen on the surface of the cell walls. From these Figures it appears easier for the bone to grow within the undersintered microstructure than the fully densified structure.

Example II

The method of Example I was repeated except that the rate of addition of the initiator and the catalyst were selected so that the time before onset of polymerisation was 16 minutes instead of 1.5 minutes. A highly porous foam exhibiting a larger cell size as shown in Figure 7 resulted. It can be seen from the different Figures that the time before the onset of polymerisation has had a major influence on the cell structure.

The Figures of the accompanying drawings are microphotographs as follows:

Figure 1 is a general foam;

Figure 2 is a foam produced in Example I taken after an idle time of 1.5 minutes;

Figure 3 is the polymerised foam of Example I fired at 1250°C for 2 hours;

Figure 4 is the polymerised foam of Example I fired at 1350°C for 2 hours;

Figure 5 is the fired product shown in Figure 3 after being immersed in a bone cell culture for 36 hours;

Figure 6 is the fired product shown in Figure 4 after being immersed in a bone cell culture for 36 hours; and

Figure 7 is the foam produced in Example II.

CLAIMS

1. A method of making a porous article composed of bonded particles (such as hydroxyapatite or the like) the method comprising the steps of:
 - a) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
 - b) forming a foam of the dispersion;
 - c) polymerising the foamed structure;
 - d) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles, and
 - e) firing the article to remove the organic binder and provide a ceramic bond

characterised in that small bubbles of gas are introduced in the dispersion with agitation to form the foam and are allowed to coalesce before the polymerisation of the monomeric material.
2. A method according to Claim 1, wherein the dispersion comprises particles having an average particle size less than 5 micrometres and preferably 95% of the particles are less than 2 micrometres.

3. A method according to Claim 1 or 2, wherein the particles are hydroxyapatite, oxides and non-oxides such as alumina, mullite, silicon carbide, silicon nitride, zirconia, titanium oxide; and the like.
4. A method according to any preceding Claim, wherein the content of the solids in the dispersion is 10% to 90% by weight.
5. A method according to Claim 4, wherein the content of solids is 40% to 80% by weight.
6. A method according to any preceding Claim, wherein the liquid carrier is water or organic liquid or a mixture.
7. A method according to any preceding Claim, including the step of adding a dispersing agent to the dispersion.
8. A method according to any preceding Claim including the step of controlling the onset of polymerisation by adjustment of the addition levels of the initiator and catalyst for polymerisation of the monomer.
9. A method according to any preceding Claim, wherein the onset of polymerisation is controlled by adjustment of the concentration of oxygen.
10. A method according to Claim 8 or 9, wherein the period until onset of polymerisation is between an instantaneous polymerisation and 20 minutes.
11. A method according to any preceding Claim, including the step of applying a partial vacuum to a foam before the commencement of polymerisation until

after the end of polymerisation, after which the foam is brought back to atmospheric pressure.

12. A method according to any preceding Claim, wherein the product is subjected to drying and firing to form a porous ceramic article.
13. A method according to Claim 12, including the subsequent step of growing bone cells in the porous ceramic product.
14. A method according to Claim 12, wherein the ceramic article has pore sizes greater than 150 micrometres.
15. A method according to Claim 12, including adding a drug to the pores of the article.
16. A method of making a porous article composed of bonded particles, the method comprising the steps of:
 - a) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
 - b) forming a foam dispersion;
 - c) polymerising the foamed structure;
 - d) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles, and

- e) firing the article to remove the organic binder and provide a ceramic bond

characterised in that small bubbles of gas are introduced in the dispersion with agitation to form the foam and are allowed or caused to coalesce before the polymerisation, and in that the firing is carried out at a temperature appropriate to the growth of bone cells.

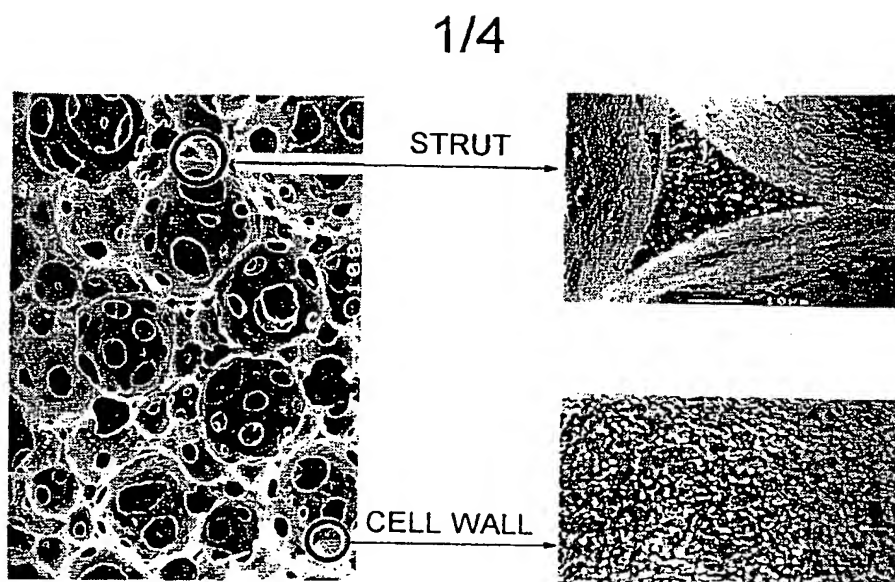


FIG. 1

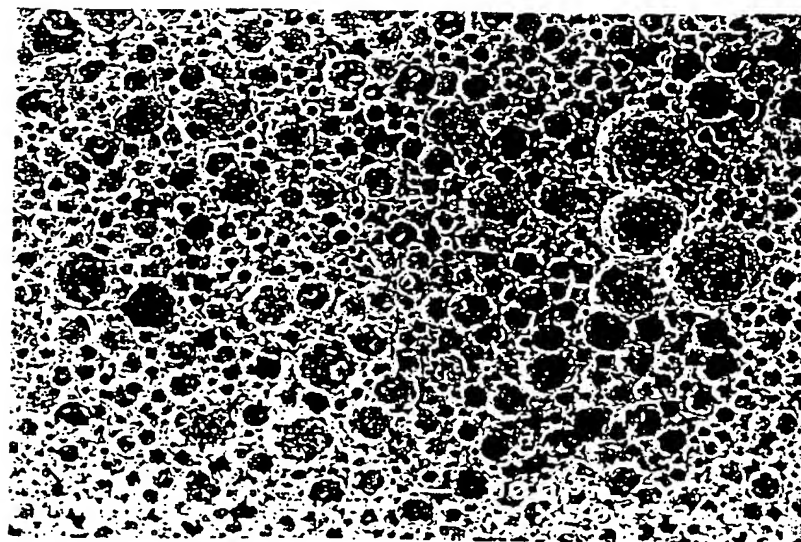


FIG. 2

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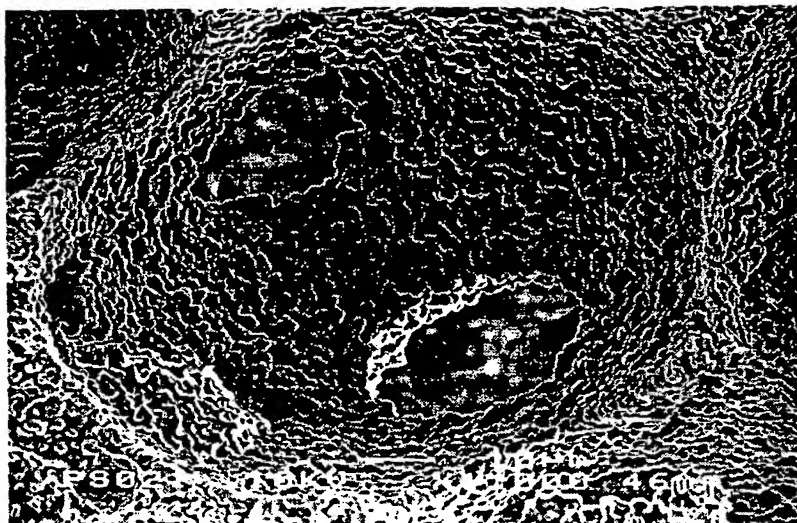


FIG. 3



FIG. 4

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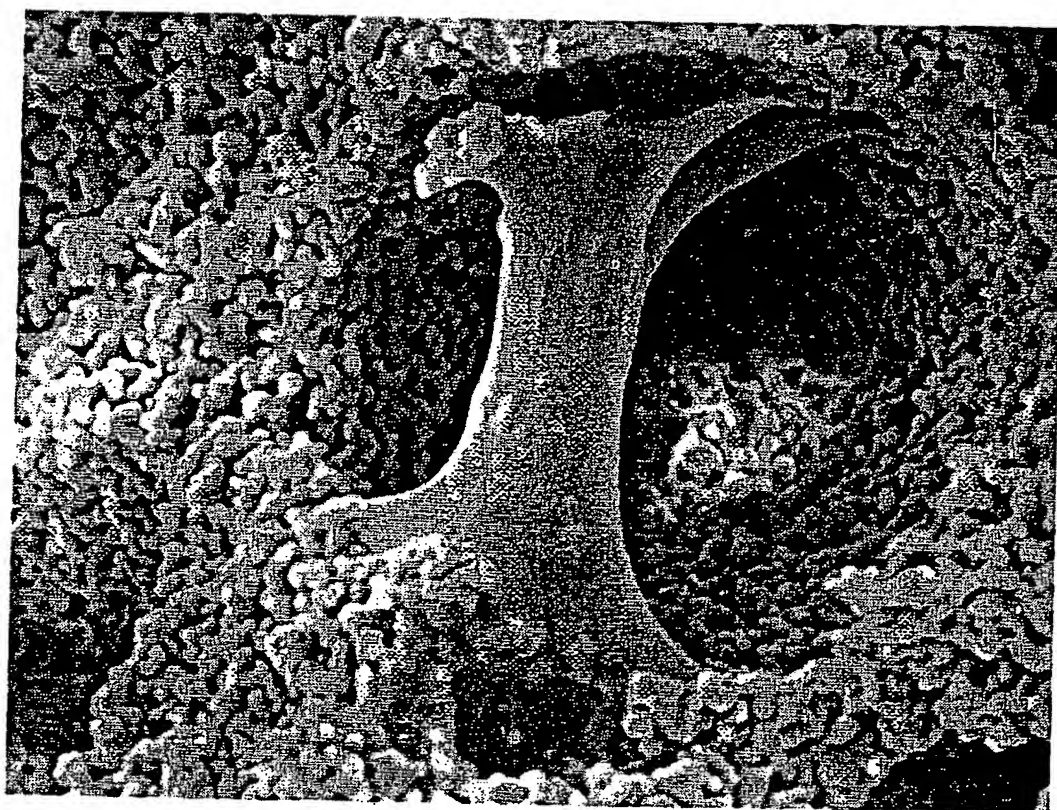


FIG. 5

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FIG. 6

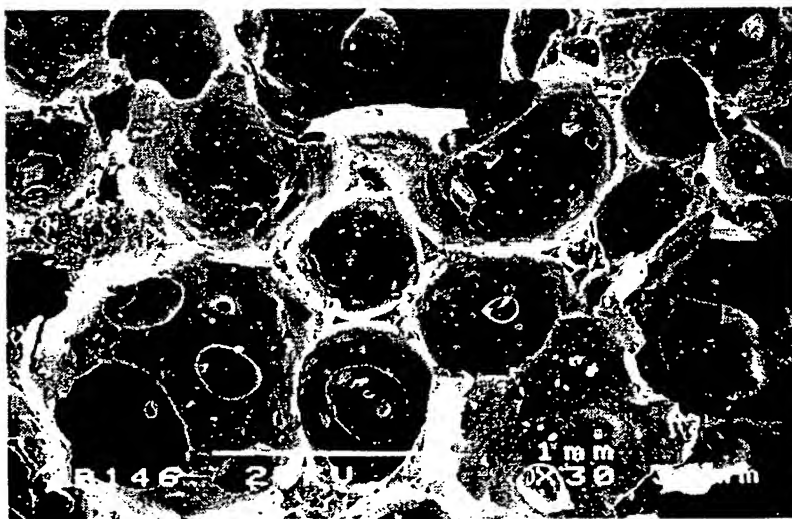


FIG. 7

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02705

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C04B38/06 A61L27/00 A61K6/033 C08J9/30

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C04B A61L A61K C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 04013 A (DYTECH) 4 March 1993 cited in the application see page 5, line 9 - page 6, line 13 see page 7, line 5 - page 8, line 21 see page 10, line 7-11 see page 10, line 22-25 see claims 31-46; examples IX,X ---	1-8,10, 12,13
A	WO 95 30631 A (DYTECH) 16 November 1995 cited in the application see claims ---	1,3-8
A	GB 2 289 466 A (DYTECH) 22 November 1995 see claims 1,2,6,9,10 ---	1,3-6,8, 10,12
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

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Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Daeleman, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/02705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Section Ch, Week 9631 Derwent Publications Ltd., London, GB; Class A18, AN 96-308081 XP002035476 ANONYMOUS: "Re-oxygenation during the polymerisation of vinyl monomer MEHQ - by purging with inert gas or reducing solubility of oxygen under partial vacuum, allowing time for adequate mixing" see abstract & RESEARCH DISCLOSURE, vol. 386, no. 003, 10 June 1996, EMSWORTH, GB,</p>	9
A	<p>DE 31 08 387 A (TOYO RUBBER INDUSTRY) 21 January 1982 see page 8, line 26-26 see page 15, line 17 - line 19 see claims 1,2</p>	1,3-7,12
A	<p>US 5 011 495 A (J. O. HOLLINGER) 30 April 1991 see column 6, line 3-15; claim 1</p>	1,13,15
A	<p>US 4 218 255 A (P.K. BAJPAI) 19 August 1980 see column 5, line 15-22 see claim 1</p>	1,15
A	<p>EP 0 058 867 A (MUNDIPHARMA GMBH) 1 September 1982 see claim 1</p>	1,15
A	<p>FR 1 580 935 A (UNIROYAL) 12 September 1969 see claim 1</p>	1
A	<p>GB 2 142 919 A (SUMITOMO) 30 January 1985 see page 1, line 109-117; claim 1</p>	
A	<p>DE 43 13 715 A (RÖHM GMBH) 3 November 1994</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9304013 A	04-03-93	AT 132124 T AU 2405492 A DE 69207198 D DE 69207198 T EP 0598783 A ES 2081126 T JP 7501307 T US 5563106 A	15-01-96 16-03-93 08-02-96 25-07-96 01-06-94 16-02-96 09-02-95 08-10-96
WO 9530631 A	16-11-95	AU 2415095 A EP 0759018 A GB 2289272 A	29-11-95 26-02-97 15-11-95
GB 2289466 A	22-11-95	AU 2415195 A BR 9507674 A EP 0759020 A WO 9530633 A US 5705448 A	29-11-95 19-08-97 26-02-97 16-11-95 06-01-98
DE 3108387 A	21-01-82	JP 56145153 A CA 1158424 A US 4472332 A	11-11-81 13-12-83 18-09-84
US 5011495 A	30-04-91	NONE	
US 4218255 A	19-08-80	NONE	
EP 58867 A	01-09-82	DE 3106445 A DE 3126273 A DE 3133015 A DE 3133016 A CA 1195615 A DK 52382 A,B, US 4610692 A	04-11-82 20-01-83 10-03-83 10-03-83 22-10-85 21-08-82 09-09-86
FR 1580935 A	12-09-69	AT 295169 A CH 493588 A DE 1778498 A GB 1196090 A NL 6806362 A	15-11-71 15-07-70 05-08-71 24-06-70 19-11-68

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 1580935 A		SE 346495 B US 3537947 A	10-07-72 03-11-70
GB 2142919 A	30-01-85	JP 1789574 C JP 4070026 B JP 60018174 A JP 1823720 C JP 2054303 B JP 60016879 A AU 3041484 A DE 3425182 A FR 2548661 A HK 14889 A NL 8402158 A SE 461393 B SE 8403619 A SE 465774 B SE 8804478 A SE 465775 B SE 8804479 A SE 465776 B SE 8804480 A US 4963145 A US 4654314 A	29-09-93 09-11-92 30-01-85 10-02-94 21-11-90 28-01-85 10-01-85 24-01-85 11-01-85 24-02-89 01-02-85 12-02-90 10-01-85 28-10-91 12-12-88 28-10-91 12-12-88 28-10-91 12-12-88 16-10-90 31-03-87
DE 4313715 A	03-11-94	CH 686517 A FR 2704552 A GB 2277931 A,B IT T0940332 A,B NL 9400413 A	15-04-96 04-11-94 16-11-94 27-10-94 16-11-94